510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE AND INSTRUMENT TEMPLATE

A. 510(k) Number:
k041635

B. Purpose for Submission:
New device

C. Analyte:
Glycosylated hemoglobin A1c (HbA1c)

D. Type of Test:
Quantitative affinity chromatography

E. Applicant:
Provalis Diagnostics Ltd

F. Proprietary and Established Names:
G5 I HbA_{1c} and G5 II HbA_{1c} Test System

G. Regulatory Information:

1. Regulation section:
   21 CFR §862.7470, Assay, glycosylated hemoglobin
   21 CFR §864. 8625, Control, hemoglobin
2. Classification:
   Class II
   Class II (performance standards)
3. Product Code:
   LCP Glycosylated hemoglobin assay
   GGM Control, hemoglobin
4. Panel:
   Hematology (81)

H. Intended Use:

1. Intended use(s):
   See indications for use below.
2. Indication(s) for use:

G5 I HbA_{1c} Test System:

"The G5 I HbA1c Test is an affinity chromatography method and is intended for the in vitro quantitative determination of HbA1c in capillary blood taken from a fingerprick or whole blood in EDTA.

G5 I HbA1c Test System is indicated for monitoring the time averaged blood glucose levels of known diabetics, for professional use as an indicator of overall glycemic control.

The G5 I HbA1c Test System consists of the HbA1c test cartridge, the G5 Instrument, the G5 System Check Cartridge and the G5 HbA1c Quality Controls.

The G5 I HbA1c Test System is intended for use in a physicians/doctors office."

G5 II HbA_{1c} Test System:
"The G5 II HbA1c Test is intended for testing blood taken from a fingerprick.

G5 II HbA1c Test System shows how good glucose control has been over a two to three month period.

The G5 II HbA1c Test System consists of the HbA1c test cartridge, the G5 Instrument, the G5 System Check Cartridge and the G5 HbA1c Quality Controls.

The G5 II HbA1c Test System is intended for prescription home use."

3. Special condition for use statement(s):
   This device is intended for point-of-care settings (G5 I HbA_{1c}) and prescription home use (G5 II HbA_{1c}).
4. Special instrument Requirements:
   The cartridges are for use on the Provalis G5 A1c Testing System.

I. Device Description:

Test cartridge is for use on separately supplied instrument. The test cartridge uses boronate affinity chromatography to separate the A1c hemoglobin fraction from the non-glycosylated hemoglobin fraction. Buffers are included in the cartridge, separated from the other components by foil seals. The G5 instrument is a single wavelength photometer that measures both blood fractions and uses an algorithm to convert the result into the percentage A1c in the sample. The device also includes a G5 System Check cartridge and G5 HbA1c quality controls.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Glycosal HbA_{1c} and Glycosal II HbA_{1c} Tests
2. Predicate K number(s):
   k001392 and k011933
3. Comparison with predicate:
   The candidate device(s) and the predicate device(s) are essentially alike. They have the same intended use, the same indications for use, the same manufacturer, the same analyte, the same methodology, factory calibrations, and the same controls. They differ in the total test time (7 minutes versus 4 minutes), the number of user steps (3 steps versus 6 steps), and there have been modifications to the cartridge design, instrument ergonomics, and software.

K. Standard/Guidance Document Referenced (if applicable):

Area of Study	Reference Procedure	Procedure Title
Stability	BS EN 13640	Stability Testing of In Vitro Diagnostic Reagents

Area of Study	Reference Procedure	Procedure Title
Electrical Safety	BS EN 61010 IEC 61010	BSI Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use: General Requirements
Electrical Systems	BS EN 60601	Medical Electrical Equipment. General Requirements for Safety. Collateral Standard. Safety Requirements for Medical Electrical Systems
Controls and Calibrators	BS EN ISO 17511	In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials
Risk Management	BS EN ISO 14971	Medical devices - Application of risk management to medical devices
Precision	NCCLS EP5-A	User Evaluation of Precision Performance of Clinical Chemistry Devices

L. Test Principle:

The G5 A1c Testing System uses boronate affinity chromatography to separate the A1c fraction from the non-glycolytic hemoglobin fraction. After blood has been added to the G5 A1C cartridge, the blood cells are lysed to release the hemoglobin. In the first chamber of the cartridge, the lysate is mixed with boronate beads to bind the hemoglobin A1c. After an incubation period, the instrument turns the cartridge so the beads form a column in the center of the cartridge. The column is washed then the hemoglobin A1c is eluted from the boronate affinity beads. The instrument measures the hemoglobin A1c concentration by means of a single-wavelength photometer.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Aliquots from a frozen normal blood sample and sample with elevated HbA1c were each tested in duplicate twice a day for 20 days to determine the precision of the G5 system.

Precision of the G5 System

	Normal Sample			Abnormal Sample		
	Mean	**SD**	**%CV**	**Mean**	**SD**	**%CV**
Between Day	4.61	0.32	6.95	9.7	0.28	2.85
Within Day	4.61	0.13	2.74	9.7	0.62	6.44
Between Run	4.61	0.19	4.19	9.7	0.35	3.62
Overall	4.61	0.23	4.98	9.7	0.34	3.5

Provalis has set their acceptance criteria at ≤5 % CV for the overall precision.

Between-cartridge lot variation was assessed with three cartridge lots tested five times at three different HbA1c levels.

Variation between Cartridge Lots

	Batch 1		Batch 2		Batch 3	
	Mean ± SD	% CV	Mean ± SD	% CV	Mean ± SD	% CV
Standard 1	5.4 ± 0.1	2.7	5.3 ± 0.1	2.2	5.1 ± 0.1	2.5
Standard 2	8.8 ± 0.3	3.7	9.1 ± 0.1	1.5	8.9 ± 0.3	3.3
Standard 3	12.1 ± 0.3	2.3	12.0 ± 0.5	4.2	12.0 ± 0.2	1.8

These values were within Provalis' acceptance criteria of ≤6 % CV.

b. Linearity/assay reportable range:
Samples were made by mixing a high HbA1c sample with a normal HbA1c sample in different ratios. The samples were run in triplicate in the G5 assay on two G5 instruments. Provalis' acceptance criteria were recoveries between 95 to 105%.

Linearity of G5 Assay: Upper Range

Sample	Expected %HbA1c	Observed %HbA1c	% Recovery
Low Sample Neat	6.2	6.2	100
2	7.6	7.5	99
3	9.1	9.1	100
4	10.6	10.9	103
5	12.1	12.4	103
High Sample Neat	13.5	13.5	100

These results show that the assay is linear between 6 to 14% HbA1c.

Provalis tested the lower limits of the assay by mixing a known sample of blood from three non-diabetics (here, "low sample neat") in different ratios with a known sample of blood from three diabetics ("high sample neat"). The samples were run in replicates of five on the G5.

Linearity of G5 Assay: Lower Range

Sample	Expected %HbA1c	Observed %HbA1c	% Recovery
Low Sample Neat	4.5	4.5	100
2	5.6	5.8	105
3	6.6	6.4	96.5
4	7.7	7.7	99.8
5	8.8	8.4	96.0
High Sample Neat	9.9	9.9	100

This study demonstrates that the assay is linear between 4.5 to 10% HbA1c. Thus, the G5 assay is linear between 4.5% and 14% HbA1c in laboratory studies; however, clinical studies support a claim of linearity from 4% to 15%.

c. *Traceability, Stability, Expected values (controls, calibrators, or method):*

Results obtained with the G5 HbA_{1c} Test System are traceable to Diabetes Control and Complication Trial (DCCT), through the NGSP program.

Accelerated temperature stability testing showed that the assay cartridges are stable (< 5% CV from baseline) for 60 days at 35°C, which equates to a shelf-life of 16 months at 2-8°C. The assay cartridge is stable for one month at 15-25°C after storage at 2-8°C.

Controls were cleared under k952720. They are traceable to a DCCT aligned method. The control solutions are stable for 13 months at 2-8°C; once opened they are stable for 7 days at 2-8°C.

d. *Detection limit:*
Not applicable since normal blood will have between 4 to 6% HbA1c. Data presented above supports a linearity claim down to 4% HbA1c.

e. *Analytical specificity:*
Fresh finger-stick and EDTA whole blood were collected from five volunteers and run in duplicate. EDTA whole blood was also tested at Day 4 and Day 5 post-collection. Both fresh blood and EDTA whole blood were comparable at Day 1. EDTA-treated whole blood at Day 4 and 5 was comparable to EDTA-treated blood at Day 1 (when stored at 2-8°C). Thus, both fresh finger-stick and EDTA samples up to 5 days old can be tested with the G5 assay.

The sponsor tested the effect of variation in hemoglobin and hematocrit levels by comparing assay recovery at three hematocrit levels (30%, 45%, and 60%) and at three total hemoglobin levels (8.9 g/dL, 13.6 g/dL, and 19.6 g/dL). Each condition was tested five times and the results were averaged. The results were comparable in all conditions (%CV<6%), suggesting that the assay will perform acceptably over the normal range of hemoglobin and hematocrit levels.

The sponsor tested whether acetaminophen, aspirin, caffeine, hydroxyzine (a sedative antihistamine), triglycerides, or bilirubin levels at or slightly above physiological levels interfere with assay performance. The drugs were all tested at 300 ug/mL while the triglycerides and bilirubin were tested at several concentrations. Samples across a range of HbA1c were spiked with varying levels the various compounds and assayed in triplicate or

quadruplicate. None of the compounds at the levels tested affected recovery of HbA1c by the assay.

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:
A method comparison study was performed at a regional clinic in the UK. This study compared fresh capillary finger-stick samples and venous EDTA-preserved samples tested with the G5 assay system to the predicate (Glycosal) and to the BioRad Variant, a clinical laboratory based method. Seventy-four individuals with Type I, Type II, or no diabetes provided samples that were tested by Provalis technicians.

Comparison of G5 assay to other methods

G5 sample	Other Method	Linear Regression	R^2	r value
Fresh capillary finger-stick	G5 - venous EDTA	y = 0.974x + 0.13	0.92	0.96
	Glycosal – venous EDTA	y = 0.938x – 0.43	0.92	0.96
	Variant – venous EDTA	y = 0.855x + 0.45	0.92	0.97
Venous EDTA	Glycosal – venous EDTA	y = 0.966 – 0.69	0.95	0.96
	Variant – venous EDTA	y = 0.881x + 0.22	0.94	0.97

This study suggests that the G5 assay performs comparably to other methods of determining %HbA1c.

b. Matrix comparison:
See Section M.1.e above for comparison of fresh finger-stick blood and venous EDTA-preserved blood.

3. Clinical studies:

a. Clinical sensitivity:
Point of Care Clinical Trials:
The ability of untrained, non-laboratory physician's office staff to run the G5 I assay was tested at three sites, one in the US with three untrained operator participants and two in the UK, each with one untrained operator participant. Office staff participants reviewed the package insert and ran no more than two practice samples prior to starting the study. Their results were compared to results obtained by a trained Provalis staff member who ran the samples in parallel with the untrained operator. Ten fresh finger-stick and

ten stored venous samples were obtained from diabetic patients or non-diabetic office staff at each study site; either three or five known control samples were run in triplicate by each operator at each site.

Summary of Physician Office Study Site Results (G5 I)

Site - operator	Regression Equation	r value	Mean % CV*
US Site – operator 1	y = 0.90x + 0.65	0.97	3.1%
US Site – operator 2	y = 0.85x +1.03	0.96	4.6%
US Site – operator 3	y = 1.01x + 0.11	0.96	4.0%
UK Site 1	y = 0.95x + 0.45	0.95	4.6%
UK Site 2	y = 1.00x – 0.01	0.96	3.3%

* trained and individual untrained operator

Application of the regression equations at several levels revealed that operator bias ranged between no bias (UK Site 2) and a 6% bias at normal HbA1c levels (5% HbA1c) and a -8% bias at a highly elevated Hb1A1c level (15% HbA1c) (US Site, operator 2). It is not expected that this latter level of bias would change medical decisions about diabetes management.

'Home-Use' Study:
The ability of untrained lay people to run the G5 II assay was assessed at three diabetes clinics in the US. There were 159 participants (142 had diabetes, of which 65% had type II diabetes) recruited the patients population at each clinic. The participants were divided roughly equally between each study site and equally by sex. Participants were provided with test instruction booklets, a quick reference guide, and asked to watch a training video. They ran a control disc to check the system, the tested their own blood by capillary finger-sticks in duplicate. A trained operator also tested the patient once by finger-stick during the visit. In total, 8 volunteers (5%) failed to get a result on one of their two tests. These errors were recorded as device time-out or device errors.

Summary of Home User Study Site Results (G5 II)

Site	Regression Equation	n =	r value
San Mateo CA	y = 0.913x + 0.57	104	0.96
Concord CA	y = 0.936x + 0.35	108	0.93
San Antonio TX	y = 0.932x + 0.60	106	0.96
Overall	y = 0.929x + 0.49	318	0.96

b. Clinical specificity:
Not applicable.

c. Other clinical supportive data (when a and b are not applicable):

4. Clinical cut-off:
Not applicable.

5. Expected values/Reference range:
The normal range for HbA1c in non-diabetic people is 4 to 6%. The American Diabetes Association recommends a goal of <7% for effective management of diabetes and to minimize long-term diabetic complications. A level above 7% suggests that more intensive diabetes management should be considered.

N. Instrument Name:
G5 Reader

O. System Descriptions:

1. Modes of Operation:
Automatic after manual sample load
2. Software:
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:
Yes ____√____ or No _____
3. Sample Identification:
No direct sample identification.
4. Specimen Sampling and Handling:
Manual loading of single whole blood sample
5. Assay Types:
Affinity chromatography separation
6. Reaction Types:
Single wavelength photometry of hemoglobin fractions
7. Calibration:
The G5 instrument is calibrated by the manufacturer to deliver standardized HbA1c results.
8. Quality Control:
The System Check Cartridge is supplied with the G5 instrument to check that the optical system is working correctly. The user is advised to run it once a day before patient samples are tested, if the system has been moved, after an error message, and if there is concern that a test result is incorrect.

   Additional quality control solutions prepared from human blood (see above) are available; their use is recommended with each new delivery of cartridges.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "L. Performance Characteristics" Section of the SE Determination Decision Summary:
None noted.

Q. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.